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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/030,417

08/14/2002

Rainer H Muller

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EXAMINER

EBRAHIM, NABILA G

ART UNIT

PAPER NUMBER

1618

MAIL DATE

DELIVERY MODE

02/25/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<i>Office Action Summary</i>	Application No.		Applicant(s)	
	10/030,417		MULLER ET AL.	
	Examiner		Art Unit	
	Nabila G. Ebrahim		1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 29 August 2008.  
2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-18,20,24-34 and 36-47 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 1-18,20, 24-34, and 36-47 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.  
10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

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## DETAILED ACTION

Receipt of amendments to the claims and Applicant's remarks dated 8/28/2008 is acknowledged.

### *Status of Claims*

Claims 1-18, 20, 24-34, and 36-47 are pending in the application.

*Status of Office Action:* Final.

### *Claim Rejections - 35 USC § 102*

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

In view of amending the claims, the rejection of claims 1-4, 7, 10, 11, 13, 15, 24 and 27 remain rejected under 35 USC 102(b) as anticipated by Muller et al US 5, 858, 410 (Muller).

Muller teaches a method for preparing nanoparticles of drugs e.g., corticoids such as prednisolone (col. 22, lines 40-45), the drug particles having average size of 10-1,000 nanometers made by dispersing solid therapeutically active drugs in a solvent and subjecting the dispersion to high-pressure homogenization in a piston-gap homogenizer (abstract and col. 20, lines 23-30) at room temperature (i.e. under 90 degrees; col. 20, lines 35-40).

Claims 1-4, 7, 10, 11, 13, 15, 22 and 27 are anticipated by Muller's '410.

Instant claims reciting "water-reduced dispersion medium containing less than 80 wt% of water", the recitation would not distinguish the instant claims over the prior art because Muller teaches a method to make a drug carrier subjecting a solid therapeutically active compound dispersed in a solvent to high pressure homogenization in a piston-gap homogenizer to form particles having an average diameter of 40 nm to 100 nm wherein said active compound is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents (claim 38), note that the use of the preposition "or" means the exclusion of the aqueous

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media in the dispersion which is interpreted as a non-aqueous solvent and a percentage of 0% water and consequently, less than 80%. Regarding including the limitation of "at temperature of 20 °C or less" would not further distinguish the instant claims over the prior art since Muller teaches suspending the particles at "room temperature" which is between 20 °C to 25 °C. Thus the instant claims temperature still overlap with the prior art.

*Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-18, 20, 24-34, and 36-47 remain rejected under 35 U.S.C.103(a) as being unpatentable over Desai et al WO 98/14174 in (Desai) view of Muller US 5, 858, 410 (Muller).

Desai et al (Patent WO '174) discloses a process for preparation of microparticles or nanoparticles of water insoluble drugs; e.g. paclitaxel, an agent that is insoluble in water and uses polymers such as polylactides and polyglycolides. The drug is dissolved in an organic solvent (page 17, lines 15-25), a protein such as albumin is added to stabilize the nanoparticles (page 17, lines 31-34) and the mixture is homogenized under high-pressure homogenization

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(page 18, lines 6-15 and page 51, lines 25). In disclosing a method for making a pharmaceutically acceptable formulation, Desai discusses sterile-filtration and how drug of particle size less than 200 nm is obtained (page 19, lines 1-16, page 10, lines 24 and page 20, and lines 30-35). The drug particles can be in crystalline or amorphous form (page 13, lines 5-10); details of how to make drug particles of size less than 200 nm are provided. Furthermore, Desai et al also disclose the effect the solvent used has on drug particle size (page 38, lines 5-20) and further discuss the advantage of making the composition in the form of albumin-paclitaxel combination-low toxicity.

Regarding the amendments to the claims, the dispersion which have water-reduced dispersion medium containing less than 80 wt% of water is disclosed in Example 4 wherein the taxol is dispersed in ethanol which is free of water i.e. 0% water.

Regarding including the limitation of "at temperature of 20°C or less" would not further distinguish the instant claims over the prior art since Muller teaches suspending the particles at "room temperature" which is between 20°C to 25°C. Thus the instant claims temperature still overlap with the prior art.

Desai did not disclose the piston-gap homogenizer required in claims 44-47

Muller has been discussed hereinabove.

Therefore it would have been obvious to one of ordinary skill in the art to make paclitaxel or nanoparticles according to the methods disclosed by Desai and homogenize it in a piston-gap homogenizer because Muller teaches that it is evident that by conversion of the microparticles into nanoparticles by means of a high-energy process, to increase the surface tension to such an extent that as a result the saturation solubility increases greatly (col. 6, lines 19+). The person of ordinary skill would have expected success of having a method of preparing

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nanoparticles of an insoluble or barely soluble active agent using a high pressure homogenizing process in a piston-gap homogenizer and containing less than 80% of water.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

*Response to Arguments*

2. Applicant's arguments filed 02/28/2008 have been fully considered but they are not persuasive.

Applicant argues that:

The claim language "gentle" requires reduced or without cavitation and claims 30, 36, 37, 46 and 47 recite "without cavitation."

To respond: the word "gentle" is recited in the preamble of the claims. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. Further, gentle is a broad term and is not specifically defined in the specification, thus, would be within the scope of the prior art. Further, there is nothing in the prior art that Finally, though Applicant claims that the word "gentle" describes the force exerted during homogenization to avoid cavitation, it is noted that Desai teaches a homogenization under pressure of 3000-30,000 psi while the instant claims recite pressure of 100-2000 bare which is equal to 1450-29,000 psi.

Applicant argues that:

Desai and Muller teach away because both references teach imparting high shear and cavitation.

To respond: avoiding cavitation is not specifically recited as an active step in the claims, but only recited as a result of the homogenization process. Since the prior art teaches the same

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process, the same result thereof would be expected to occur. The claims as written do not specifically exclude cavitation in the process as argued by applicant. Further, Muller teaches using cavitation or shearing and impact forces with introduction of a high amount of energy (Summary). Thus, Muller teaches a method that excludes cavitation.

Applicant argues that:

Applicants have solved these problems by providing a far more gentler method of obtaining the same particle size without using the implosion shock waves (i.e. substantially avoiding cavitation or reducing cavitation):

- 1) reducing or eliminating the use of water; and/or
- 2) reducing the temperature of the medium being homogenized.

To respond: the temperature used in Muller also overlaps with the value recited in the claims of 20 °C or less. Further, the water amount is reduced or avoided since Muller discloses drug carrier by subjecting a solid therapeutically active compound dispersed in a solvent to high pressure homogenization in a piston-gap homogenizer to form particles having an average diameter of 40 nm to 100 nm wherein said active compound is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents (claim 38). Thus water can be excluded and alternatively, organic solvents are used. Therefore, eliminating water and reducing temperature are anticipated by Muller. Further, the resulting products are the same. If Applicant believes that these two conditions would avoid cavitation, why would not Muller method do the same?

Applicant argues that:

It is believed, without being bound to any theory, that effects other than cavitation are responsible for the observed diminution action. Contrary, to the general knowledge in the art represented by Desai and Muller, Applicants have found that cavitation is not the dominating

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diminution principle in the present invention. This is further supported by performing homogenization at lower temperatures, e.g. at 20° Celsius or below. A surprisingly similar efficiency in diminution is observed, which is contrary to the general beliefs in the art.

To respond: In re Best, 195 USPQ 430, and In re Fitzgerald, 205 USPQ 594, the court discuss the support of rejections wherein the prior art discloses the subject matter, which there is reason to believe inherently includes functions that are newly cited and instantly claimed. As explained supra, Muller followed the limitations and conditions recited in the instant claims. Whatever results accomplished by reducing water and using lower room temperature, these should be achieved by Muller's invention. If Applicant found a new theory for explaining these results, this would not impart patentability.

Applicant argues that:

Present claims 46 and 47 recite particles of "5.6  $\mu\text{m}$  or less," which are not included in Desai's particle ranges. For this reason alone, the Section 103 rejection of claims 46 and 47 should be withdrawn.

To respond: Desai discloses that the particles can be of 200 nm diameter (page 10).

Applicant argues that:

Claim 25 recites carrying out the process with the exclusion of oxygen and claim 26 recites degassing the dispersion medium before use. None of the cited references teach or suggest these limitations.

To respond: instant specification at page 8 disclosing that degassing of the dispersion medium (e.g. in a vacuum or by heating). Desai teaches that solvent is rapidly evaporated under vacuum to yield a colloidal dispersion system (page 20, 31+). The reference also teaches that the volatile component may be removed by evaporation (optionally under vacuum) (page 32, lines 17+). Note that vacuuming to exclude vapors reads on degassing including oxygen.



*Conclusion*

1. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

*Correspondence*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/  
Examiner, Art Unit 1618

/Michael G. Hartley/  
Supervisory Patent Examiner, Art Unit  
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